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Intellectual Property and Technology Law

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EPOPLUS GmbH & Co. KG26112 SC-vb
10 January 2006**Claims**

1. The use of erythropoietin and/or derivatives for production of a pharmaceutical composition containing a dose of 1 to 90 IU/kg of body weight per week, preferably 1 to 45 IU/kg of body weight per week, for prevention or treatment of diseases, wherein the erythropoietin in this dose is suitable and designed for prevention or treatment of a human or animal patient exhibiting a) at least one dysfunction of endothelial progenitor cells, b) at least one cardiovascular risk factor such as hypertension, hypercholesterolemia, elevated asymmetric dimethylarginine (ADMA) levels, increased insulin resistance or hyperhomocysteinemia and c) at least one end-organ damage, namely left ventricular hypertrophy, microalbuminuria, cognitive dysfunction, increased thickness of the intima media in the carotid artery, proteinuria or a glomerular filtration rate of 30 to 80 ml/min.

2. The use of erythropoietin and/or derivatives for production of a pharmaceutical composition containing a dose of 1 to 90 IU/kg of body weight per week, preferably 1 to 45 IU/kg of body weight per week, wherein the erythropoietin in this dose is suitable and designed for cosmetic treatment of the human or animal body, especially for treatment of wrinkles, for strengthening of the connective

tissue, for protection and tightening of the skin, for protection against harmful environmental effects, for treatment of age spots, for acceleration of reepithelialization, for acceleration of hair growth and/or as makeup foundation.

3. The use of erythropoietin and/or derivatives for production of a pharmaceutical composition containing a dose of 1 to 90 IU/kg of body weight per week, preferably 1 to 45 IU/kg of body weight per week, for production of a cosmetic preparation, especially for topical application, wherein the erythropoietin in this dose is suitable and designed for cosmetic treatment of the human or animal body, especially for treatment of wrinkles, for strengthening of the connective tissue, for protection and tightening of the skin, for protection against harmful environmental effects, for treatment of age spots, for acceleration of reepithelialization, for acceleration of hair growth and/or as makeup foundation.

4. The use of erythropoietin and/or derivatives for production of a pharmaceutical composition containing a dose of 1 to 90 IU/kg of body weight per week, preferably 1 to 45 IU/kg of body weight per week, and/or a mixture of endothelial progenitor cells with at least one cell population usable for cell therapy, wherein the erythropoietin in this dose is suitable and designed for regeneration of tissues or vessels in a human or animal body, and wherein the mixture has been brought into contact with erythropoietin in vitro prior to application.

5. The use of erythropoietin and/or derivatives for production of a pharmaceutical composition containing a dose of 1 to 90 IU/kg of body weight per week, preferably 1

to 45 IU/kg of body weight per week, and/or a mixture of endothelial progenitor cells with at least one cell population usable for cell therapy, wherein the erythropoietin in this dose is suitable and designed for regeneration of tissues or vessels in a human or animal body, and wherein the mixture [*sic: erythropoietin*] is administered before, after or simultaneously with application of the mixture.

6. The use of erythropoietin and/or derivatives for production of a pharmaceutical composition or of a kit containing a dose of 1 to 90 IU/kg of body weight per week, preferably 1 to 45 IU/kg of body weight per week, and/or at least one chemical, thermal, mechanical or biological agent, especially a pharmacological active ingredient, for production of a pharmaceutical composition or of a kit containing erythropoietin in this dosage and the at least one chemical, thermal, mechanical or biological agent, for prevention or treatment of diseases, wherein the erythropoietin in this dose is suitable and designed for sequential, timed successive or simultaneous application of the erythropoietin with the at least one chemical, thermal, mechanical or biological agent.

7. The use of erythropoietin according to claim 6, wherein the mechanical agents are endoprostheses, preferably implantation supports for teeth, bones or ligament/tendon replacements.

8. The use of erythropoietin according to claim 6, wherein the biological agents are solid organs such as liver, kidneys, heart, pancreas, skin or hair implants.

9. The use of erythropoietin and/or derivatives for production of a pharmaceutical composition containing a dose of 1 to 90 IU/kg of body weight per week, preferably 1 to 45 IU/kg of body weight per week, wherein the erythropoietin in this dose is suitable and designed for prevention or treatment of diseases, wherein the disease is hepatic disorders such as hepatitis, cirrhosis of the liver, acute or chronic liver failure, bone and cartilage disorders or lesions, mucous membrane disorders or lesions, especially in the gastrointestinal tract, Crohn's disease, ulcerative colitis, renal function restrictions with glomerular filtration rates of 30 to 80 ml/min, microalbuminuria, proteinuria, or wounds and sequelae thereof.

10. The use of erythropoietin and/or derivatives for production of a pharmaceutical composition containing a dose of 1 to 90 IU/kg of body weight per week, preferably 1 to 45 IU/kg of body weight per week, for production of a kit containing erythropoietin, endothelial progenitor cells and at least one cell population usable for cell therapy, wherein the erythropoietin is preferably present in low dosage.

11. The use according to one of claims 1 to 10, wherein the pharmaceutical composition is used for stimulation of physiological mobilization of endothelial progenitor cells,

proliferation of endothelial progenitor cells, differentiation of endothelial progenitor cells to endothelial cells and/or migration of endothelial progenitor cells toward a vasculogenic or angiogenic stimulus.

12. The use according to claims 1 to 11, wherein the adhesion ability of endothelial progenitor cells undergoing differentiation is increased.

13. The use according to claims 1 to 12, wherein the stimulation of endothelial progenitor cells leads to formation of endothelial tissue.

14. The use according to one of claims 1 to 13, wherein the stimulation of endothelial progenitor cells leads to formation of new blood vessels.

15. The use of erythropoietin in a low dosage of 1 to 90 IU/kg of body weight per week for the therapy of pathological states or diseases of the human or animal body associated with a dysfunction of endothelial progenitor cells, and wherein the pathological states or diseases associated with a dysfunction of endothelial progenitor cells are hepatic disorders such as hepatitis, cirrhosis of the liver, acute or chronic liver failure, bone and cartilage disorders or lesions, mucous membrane disorders or lesions, especially in the gastrointestinal tract, Crohn's disease, ulcerative colitis, renal function restrictions with glomerular filtration rates of 30 to 80 ml/min, microalbuminuria, proteinuria, elevated ADMA levels or wounds and sequelae thereof.

16. The use according to claim 15, wherein the dysfunction of the endothelial progenitor cells consists of their impaired proliferation ability, their impaired ability to differentiate to endothelial cells, their impaired adhesion ability and/or their impaired ability to migrate toward a vasculogenic or angiogenic stimulus.
17. The use according to claim 15 or 16, wherein the dysfunction of endothelial progenitor cells impairs or prevents the formation of endothelial tissue and/or blood vessels.
18. The use according to one of claims 15 to 17, wherein the dysfunction of endothelial progenitor cells has a pathogenic cause.
19. The use of erythropoietin in a low dose, especially of 1 to 90 IU/kg of body weight per week, for the therapy of hepatic disorders such as hepatitis, cirrhosis of the liver, acute or chronic liver failure, bone and cartilage disorders or lesions, mucous membrane disorders or lesions, especially in the gastrointestinal tract, Crohn's disease, ulcerative colitis, renal function restrictions with glomerular filtration rates of 30 to 80 ml/min, microalbuminuria, proteinuria, elevated ADMA levels or wounds and/or sequelae thereof.
20. The use according to one of claims 1 to 19, wherein erythropoietin is administered to each patient in a dose of 1 to 90 units/kg of body weight per week.
21. The use according to claim 20, wherein erythropoietin is administered to each patient in a dose of 1 to 45 units/week.

22. The use according to one of claims 1 to 21, wherein the pharmaceutical composition is suitable for parenteral, especially intravenous, intramuscular, intracutaneous or subcutaneous as well as topical administration.
23. The use according to claim 22, wherein the pharmaceutical composition has the form of an injection or infusion.
24. The use according to one of claims 1 to 21, wherein the pharmaceutical composition is suitable for pulmonary administration.
25. The use according to claim 24, wherein the pharmaceutical composition has the form of an aqueous solution, a nonaqueous solution or a powder.
26. The use according to claim 24 or 25, wherein the pharmaceutical composition has the form of an aerosol preparation.
27. The use according to one of claims 1 to 21, wherein the pharmaceutical composition is suitable for oral administration.
28. The use according to claim 27, wherein the pharmaceutical composition has the form of a solution, suspension, emulsion or tablet.
29. The use according to one of claims 1 to 28, wherein the pharmaceutical composition contains at least one further active ingredient for stimulation of endothelial progenitor cells.

30. The use according to claim 29, wherein the further active ingredient is VEGF, PIGF, GM-CSF, an ACE inhibitor, an AT-1 blocker, an HMG-CoA reductase inhibitor and/or an NO donor.

31. The use according to claim 30, wherein the HMG-CoA reductase inhibitor is a statin such as simvastatin, mevastatin or atorvastatin, the ACE inhibitor is an active ingredient such as enalapril, ramipril or trandolapril and/or the AT-1 blocker is an active ingredient such as irbesartan, lortsartan or olmesaratan.

32. The use of erythropoietin for production of a transplantable endothelial preparation.

33. The use according to claim 32, wherein endothelial cells are produced in vitro by cultivation of endothelial progenitor cells in the presence of erythropoietin in a small dose, namely of 0.001 to 90 IU/kg/week.

34. The use according to claim 32 or 33, wherein the cultivation of the endothelial progenitor cells takes place in the presence of at least one further active ingredient selected from the group comprising VEGF, PIGF, GM-CSF, an ACE inhibitor such as enalapril, ramipril or trandolapril, an AT-1 blocker such as irbesartan, lortsartan or olmesaratan, an HMG-CoA reductase inhibitor, especially simvastatin, mevastatin or atorvastatin, and an NO donor, especially L-arginine.

35. The use according to one of claims 1 to 34, wherein erythropoietin is human or animal erythropoietin.

36. The use according to claim 35, wherein erythropoietin is a derivative, an analog, a modification or a mutein of erythropoietin.

37. The use according to claim 35 or 36, wherein erythropoietin is isolated from human urine, from the urine or plasma of patients suffering from aplastic anemia, from tissue cultures of human renal cancer cells, from human lymphoblast cells, which have the ability to produce human erythropoietin, or from a hybridoma culture obtained by cell fusion of a human or animal cell line.

38. The use according to claim 35 or 36, wherein erythropoietin is an erythropoietin produced by means of DNA recombination techniques.

39. A pharmaceutical composition for stimulation of endothelial progenitor cells, for stimulation of the formation of endothelial tissue, for stimulation of vasculogenesis and/or for treatment of diseases or pathological states associated with a dysfunction of endothelial progenitor cells, comprising erythropoietin and/or a derivative, an analog, a modification or a mutein thereof as the active ingredient as well as at least one further active ingredient selected from the group comprising VEGF, PIGF, GM-CSF, an ACE inhibitor such as enalapril, ramipril or trandolapril, an AT-1 blocker such as irbesartan, Iorsartan or olmesartan, an HMG-CoA reductase inhibitor and an NO donor, preferably in a low dose, especially of 1 to 90 IU/kg of body weight per week.

40. A pharmaceutical composition for prevention and/or therapy of hepatic disorders such as hepatitis, cirrhosis of the liver, acute or chronic liver failure, bone and cartilage disorders or lesions, ligament and tendon disorders or lesions, mucous membrane disorders or lesions, especially in the gastrointestinal tract, Crohn's disease, ulcerative colitis, renal function restrictions with glomerular filtration rates of 30 to 80 ml/min, microalbuminuria, proteinuria, elevated ADMA levels or wounds and sequelae thereof, comprising erythropoietin and/or a derivative, an analog, a modification or a mutein thereof as the active ingredient, preferably in a small dose, especially of 1 to 90 IU/kg of body weight per week.
41. A pharmaceutical composition according to claim 40, additionally including at least one further active ingredient selected from the group comprising VEGF, PIGF, GM-CSF, an ACE inhibitor such as enalapril, ramipril or trandolapril, an AT-1 blocker such as irbesartan, lortsartan or olmesartan, an HMG-CoA reductase inhibitor and an NO donor.
42. A pharmaceutical composition according to claim 39 or 40, wherein the HMG-CoA reductase inhibitor is a statin such as simvastatin, mevastatin or atorvastatin, the ACE inhibitor is an active ingredient such as enalapril, ramipril or trandolapril and/or the AT-1 blocker is an active ingredient such as irbesartan, lortsartan or olmesartan.
43. A pharmaceutical composition according to claim 39 or 41, wherein the NO donor is L-arginine.

44. The use of erythropoietin according to claims 1 to 43 for production of a pharmaceutical composition for prevention or treatment of diseases, wherein the erythropoietin and/or the pharmaceutical composition is suitable and designed for morning application to a human or animal body in a period from 6:00 to 10:00 a.m.
45. A kit containing erythropoietin, endothelial progenitor cells and at least one cell population usable for cell therapy, wherein the erythropoietin is preferably present in low dosage.
46. The use of erythropoietin and/or derivatives for production of a pharmaceutical composition or of a kit containing a dose of 1 to 90 IU/kg of body weight per week, preferably 1 to 45 IU/kg of body weight per week, for prevention or treatment of diseases of the human or animal body, wherein the erythropoietin in the said low dose is suitable and designed for improving, especially for promoting and/or accelerating, the integration of a mechanical or biological agent, especially an endoprosthesis, especially an implant, for example a tooth implant, a tooth replacement, a bone implant, a bone replacement, especially a joint prosthesis, a ligament/tendon replacement, such as the cruciate ligaments, or a solid organ into the implant or the body structures surrounding the endoprosthesis.
47. The use according to claim 46, wherein the pharmaceutical preparation or the kit additionally contains a cell therapeutic, especially endothelial progenitor cells and/or

other cell populations usable for cell therapy for regeneration of tissues and vessels.

48. The use according to one of claims 46 or 47, wherein the endoprosthesis is made of steel, ceramic, plastic or another matrix material.

49. A kit containing erythropoietin in a dose of 1 to 90 IU/kg of body weight per week, preferably 1 to 45 IU/kg of body weight per week, an endoprosthesis and if necessary a cell therapeutic, preferably endothelial progenitor cells or other cell populations usable for cell therapy.

50. The use of erythropoietin and/or derivatives for production of a pharmaceutical composition containing a dose of 1 to 90 IU/kg of body weight per week, wherein the erythropoietin in this dose is suitable and designed for prevention or treatment of insulin resistance.

51. The use of erythropoietin and/or derivatives according to one of claims 15 to 18 for production of a pharmaceutical composition containing a dose of 1 to 90 IU/kg of body weight per week, wherein the erythropoietin in this dose is suitable and designed for prevention or treatment of insulin resistance.

52. The use of erythropoietin in a small dose of 1 to 90 IU/kg of body weight per week for therapy of insulin resistance.

53. A pharmaceutical composition for prevention and/or therapy of insulin resistance, comprising erythropoietin

and/or a derivative, an analog, a modification or a mutein thereof as the active ingredient, preferably in a small dose, especially of 1 to 90 IU/kg of body weight per week.